## I. REMARKS

Claims 1-24 are pending in the application and claim 20 has been withdrawn from consideration as non-elected subject matter. Claims 1-19 and 21-24 have been rejected. Applicants respectfully traverse the rejection of claims 1-19 and 21-24.

Applicants have provided a new Declaration, which they believe to be in compliance with 37 C.F.R. § 1.67(a). The post office address has been supplied for each inventor. Applicants believe this moots the Examiner's objection.

### A. Introduction

The claimed technology is directed to transgenic, non-human mammals comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said non-human mammal. The claimed animals survive on human hemoglobin alone. Many of the techniques needed to make and use these transgenic animals were present in the art for years before Applicants' application, but those skilled in the art lacked the motivation and expectation of success that a non-human mammal could live on human hemoglobin alone.

As will be discussed below, the specification, through the detailed description of the claimed transgenic mouse system, provides general requirements needed to practice the claimed subject matter in other non-human mammals. Once Applicants outlined these general requirements and once Applicants showed that the claimed subject matter would work as claimed one of skill in the art would understand, based on the specification and the knowledge of the skilled artisan, how to practice the full scope of the claimed subject matter.

Methods and materials for making transgenic mice and knockout mice existed for years before the filing of the present application. Furthermore, methods and materials for making the full scope of claimed non-human mammals, unique to other non-human mammals, also existed at the time of the application, and were well known to the skilled artisan. The contribution of the Applicants, in part, arises from the fact that prior to the present application no mammal, other than human of course, survived on human hemoglobin alone. As is discussed below, those of skill in the art, did not expect that any mammal other human, mouse or otherwise, would be able to survive in such a way. The oxygen affinities of cross species hemoglobin, the homologies of

hemoglobin, and the very precise requirements needed for overall oxygen delivery systems indicated that the mouse reduced to practice in the present application would not have a reasonable expectation of survival. Once, however, this mouse amazingly did survive, the relationship of the mouse hemoglobin to human hemoglobin and the metabolic relationship between the mouse and humans, as well as other non-human mammals taught the skilled artisan that other non-human mammals could be made using known techniques because they too would be expected to survive on human hemoglobin alone, if a mouse was so able.

**B. Rejection Under 35 U.S.C. § 112, ¶ 1**

The Office Action dated December 10, 2001, rejected claims 1-19 and 21-24 under 35 U.S.C. § 112, ¶ 1, for allegedly not being enabled for "a transgenic, non-human mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said non-human mammal." [and thus the specification allegedly] "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims."

Applicants understand that the Office Action relies on three arguments to support a rejection of non-enablement. First the PTO argues that the claimed technology requires ES cell technology and that ES cell technology did not exist for mammals other than mouse at the time of the application. Second, the PTO argues that the constructs employed by Applicants are not capable of predictably working in mammals other than mouse. Third, the PTO argues that the claims should be limited to claims requiring a hemoglobin switching construct.

Provided with this Response is a Declaration by Dr. Tim Townes, ("Townes Declaration 1") setting forth that which was known by the skilled artisan at the time of the application with respect to making the claimed non-human mammals and concluding that the skilled artisan was enabled to make non-mouse mammals as claimed, based on the specification and that which was known in the art at the time of the application. Also provided is a second declaration by Dr. Townes ("Townes Declaration 2) that sets forth the molecular biology of hemoglobin transgenes which shows that 1) those of skill in the art would expect hemoglobin transgene constructs to

work in mammals other mouse, once success was achieved in the mouse, and 2) that a switching construct is not necessary for a general hemoglobin transgene.

*1. **Specification enables making of non-mouse mammals***

As pointed out by the PTO, the claimed animals require the knocking out of the native alpha and beta hemoglobin genes and additionally require the insertion of a transgene capable of expressing the human alpha and beta globin genes. Also pointed out by the PTO, to make a knock out of any gene in a mammal one must be able to culture the cell within which the knockout event is to take place because the frequency of the required homologous recombination is very rare. The cell wherein the target gene has been knocked out, must then be able to give rise to a germ cell in an adult organism. The most developed technology in mice to perform these steps is ES technology, however, it is not true that ES cell technology is required to perform these steps, in mouse or any other mammal.

*a) Claimed mammals could be produced via nuclear transfer at the time of the priority application*

At the time of the priority application, March 6, 1996, means other than pure ES technology existed for making the claimed non-human mammals. The non-human mammals could be made via nuclear transfer. (See the Stice Declaration) Nuclear transfer provides the ability to culture cells, within which genetic manipulations, such as homologous recombination knockout technology, can be performed, and the manipulated cells, after culturing, can then be used to generate whole animals.

The Office Action states at page 5, "As the claims require introduction of a knockout construct into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenics." Respectfully, not a single claim has as the element "introduction of a knockout construct into an ES cell." The claims fail to list this limitation because the animals of the claims can be produced by a variety of methods and need not be produced by mouse "ES cell" technology. (Townes Declaration 1)

It is important to note that applicants are the first to make the claimed animals. Such animals represent a significant step in the art. Thus, it does not matter than if applicants teach all

ways to make such an animal. It is sufficient if one skilled in the art could make the claimed animal by any method.

What the specification does provide is the knowledge and direction to make a knockout of the endogenous alpha and beta globin genes in a mammal and provide in a transgenic construct human alpha and beta globin constructs. As discussed in the Townes Declaration 1, those skilled in the art of culturing cells and making whole animals from the cultured cells could have used nuclear transfer technology to produce the claimed animals, as of March 6, 1996 (Townes Declaration 1). Thus, the specific methods recited in the specification merely provide one way to make the claimed mammals.

As pointed out by the PTO, what is required to make the cells containing the alpha and beta globin constructs is the ability to culture cells, which can then be used to produce a whole animal, including germ cells in the whole animal carrying the nuclear material of the cultured cell. Dr. Townes, points out that as of January 1996, the scientific community concerned with making whole animals from cultured cells knew how to culture donor cells (cells which can be manipulated by, for example, knockout technology), such as fetal fibroblasts, under conditions which would allow for subsequent nuclear transfer of the nucleus from the cultured donor cell (Townes Declaration 1). Furthermore, this scientific community also knew how to prepare and manipulate oocytes, such that the oocytes could receive a donor nucleus (Townes Declaration 1). Lastly, this scientific community was able to take the cultured cell and fuse it to the oocyte, such that the subsequent blastocyst would develop into a full term mammal, completely based on the nuclear genetic material of the donor cell (Townes Declaration 1).

Dr. Townes concludes, "Thus, with the instructions provided in Wilmut et al., and summarized in paragraphs 9-13 above, one who produces whole animals from cultured cells would be able to make a non-mouse mammal, in addition to a mouse, from a cultured cell, based on the United States Patent Application No. 08/961,443 and that which was known in the art as of March 6, 1996" (Townes Declaration 1). This conclusion, and the facts leading to the conclusion, directly refute the PTO's position.

Therefore, a rejection under 35 U.S.C. § 112, ¶ 1 of claims 1-19, and 20-24 based on the inability to make the knockouts of the alpha and beta globin genes in mammals other than mouse because of inability to culture cells which can be used to produce a whole animal should be removed.

*b) ES like technology for non-mouse mammals existed at the time of the application*

Notwithstanding the above, ES methods for non-mouse mammals are also enabled by the specification. The PTO asserts that ES technology only existed for mice, and relies on a number of publications for support. These publications are discussed below, and it is clear that the publications actually support non-mouse ES technology. It is relevant to note that once nuclear transfer became widely available, the need to prove that ES cells could result in germ line transmission in multiple non-mouse mammalian species animals from a single cell was eliminated. Thus, one must view ES cell technology in view of other technology for producing animals from a single cell.

***(a) Moreadith et al. "Gene Targeting in Embryonic Stem Cells: the new physiology and metabolism," J. Mol. Med. 75:208-216 (1997) ("Moreadith")***

Moreadith discusses ES technology in mice. However, as noted by the Examiner, Moreadith also indicates that putative ES technology exists in other mammalian species. While the Examiner views this as indicating non-enablement for other species, Applicants assert it represents the opposite, *enablement for other species*. Moreadith provides a number of citations for non-murine ES technology, and a review of these citations shows that for hamster, pig, sheep, cattle, rabbit, rat, mink, monkey, and humans technology existed that allowed the culturing of cells which apparently could be used for knock out formation and subsequent regeneration of whole animals. "Putative" as used by Moreadith refers not to the inability of these cells to form whole animals, but rather that these cells simply had not yet been shown to do this. These cells may be formed into whole animals after manipulation, and thus provide technology that could have been used by one of skill in the art to produce the claimed animals.

***(b) Seamark, "Progress and Emerging Problems in Livestock Transgenesis: a Summary Perspective," Reprod.Fertil. Dev. 6:653-7 (1994) ("Seamark")***

Seamark actually reports that true ES technology exists for porcines. Seagate at page 654. In addition, Seamark, also clearly supports what applicants assert: mouse ES technology was not and is not the only way of making the claimed transgenic mammals. When commenting on cloning non-murine mammals Seamark states, "The alternative, more desired and, thus, preferred route towards reinstating the ES genome in the germ line which is now under active consideration by all major groups, is by means of nucleus transfer." Seamark at 655. Nucleus transfer represents an available alternative to ES cell technology because in nucleus transfer only the nucleus is transferred, not the entire cell as in ES cell technology and the nucleus is transferred to an enucleated oocyte not an early embryonic stage blastocyst, as in ES cell technology. As clearly indicated by Seamark and the papers cited therein, this technology was not and is not "putative" or "hoped for" as it existed in working form in 1994. Thus, as of at least 1994, (approximately two years before the priority application for the present application was filed) as indicated by Seamark, one of skill in the art apparently could have made animals using ES like technology.

***(c) Mullins and Mullins, "Perspective Series: Molecular Medicine in Genetically Engineered Animals Transgenesis in the Rat and Larger Mammals,"J. Clin. Invest., 98(11) S37-S40 (1996) ("Mullins")***

Mullins, as pointed out by the Examiner, states that "to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." This statement supports Applicants position that multiple technologies existed for one of skill in the art to employ when practicing the claimed subject matter. In fact this statement summarizes a paragraph in which Mullins indicates the success of techniques one of skill in the art could use to practice the claimed subject matter. Mullins states, "Freshly isolated cells from ICMs have been injected into blastocysts to produce chimeric offspring in both sheep and cattle (citation) and their totipotency at this stage is further demonstrated by their ability to produce offspring after transfer into enucleated oocytes. Mullins at S38. Mullins further states, "Such nuclear transfer techniques are potentially very

useful for the production of clonal offspring and would avoid the initial chimeric generation necessitated by the injection of ES cells into blastocysts. Id. Thus, Mullins, just like Seagate, not only indicates that ES technology existed for mammals other than mice, but nuclear transfer technology also existed. As indicated by Mullins, the skilled artisan, given the disclosure provided by the Applicants, knew how to produce the claimed animals and to employ the specific techniques created for each species of animal. The skilled artisan simply needed to know that human hemoglobin supported life in non-human mammals and Applicants provided this and more in their specification.

***2. Specification enables non-mouse transgene expression***

*a) Beta globin locus is predictive of transgene expression in mouse and other mammals and mouse data predicts success in other mammals*

**(1) PTO argues that phentotype in mouse not predictive of phentotype in other mammals**

On page 5 of the Office Action, the PTO argues "without evidence to the contrary, transgene expression in different species of transgenic non-human mammals is not predictable and varies according to the particular host species, and specific promoter/gene combinations." *Id.* at 6. The PTO further asserts, "Given such species differences in the expression of a transgene, it would have required undue experimentation to extend the results achieved in transgenic mice to the levels of transgene product in any other transgenic non-human mammal, the consequences of that production, and therefore, the resulting phenotype." *Id.* at 7. The PTO concludes by stating, "the state of the art cannot be relied upon to provide the nexus between the exemplified Hbs mice and all other transgenic non-human mammals. Applicants must provide this nexus." *Id.* at 8. Applicants respectfully disagree with each of these PTO assertions, and herein supply the requested nexus, because as discussed in detail below, the art clearly indicates that the constructs which would be used to produce the claimed animals would predictably work in not only mouse but other mammals as well and once the constructs were shown to work in mouse one of skill in the art would predict that they would work in other mammals also. Furthermore, the state of the art can be relied upon to support Applicants' position, as even the publications cited by the PTO indicate that the B-globin locus predictably causes transgene expression.

**(2) Transgenically produced intracellular protein is different than transgenically produced hormone**

As discussed by Dr. Tim Townes in his accompanying Declaration, (Townes Declaration 2) the transgenic expression of a hormone is very different, and not predictive of, the transgenic expression of an intracellular protein. The PTO relies on references to allegedly show non-enablement which are based on transgenic expression of hormones, which is not relevant to the presently claimed subject matter. As Dr. Townes states, "The levels of hormones are tightly regulated in mammals because of their potency. Since small quantities of hormones can have major phenotypic effects because of their very nature, the production of animals expressing transgenic hormones is much less predictable than the production of animals expressing non-hormonal transgenic intracellular proteins." (Townes Declaration 2). Thus, publications which allegedly indicate poor or unpredictable transgene hormone expression, such as Hammer et al., "Genetic Engineering of Mammalian Embryos," J. Anim. Sci., 63:269-78 (1986) ("Hammer") 276-277 and Ebert et al., "A Moloney MLV-Rat Somatotropin Fusion Gene Produces Biologically Active Somatotropin in a Transgenic Pig," Molecular Endocrinology 2(3):277-283 (1988) ("Ebert"), and Strojek and Wagner, "The Use of Transgenic Animal Techniques for Livestock Improvement," Genetic Engineering: Principles and Methods, 10:221-246 Plenum Press, (1988) ("Strojek"), are not relevant for the present subject matter, as the present subject matter is drawn to the production of proteins inside of erythrocytes, not the production of hormones. Transgenic hormone production is not relevant to the transgenic production of hemoglobin. As Dr. Townes states, "However, large animals that express human hemoglobin are normal. For example, Swanson et al. (Attached as Appendix A) indicate that transgenic hemoglobin was expressed at physiologically appropriate levels" (Townes Declaration 2).

**(3) PTO argues that expression in mouse not predictive of expression in other mammals**

***(a) PTO relies on publications that support expression of the constructs in the claimed animals***

**(i) Mullins and Mullins, "Perspective Series: Molecular Medicine in Genetically Engineered Animals Transgenesis in the Rat and Larger Mammals,"J. Clin. Invest., 98(11) S37-S40 (1996) ("Mullins")**

Mullins states, "Position-independent copy number-related expression can be achieved using sequences such as the locus control regions identified upstream of the Beta globin gene cluster and downstream of the CD2 gene." Mullins further states, "Such elements have been shown to *function across species barriers*, and their incorporation into gene constructs can overcome position effects and improve expression of heterologous genes within specific cell types." (emphasis added)

Mullins deals with expression of the transgene constructs and the statement cited by the PTO on page 7 of the Office Action does not refer to phenotypes as asserted by the Office but rather refers to the expression of the transgene. As discussed above, the constructs contained within the claimed transgenic animals do not have the problems discussed by Mullins.

**(ii) Wall et al., "Transgenic Livestock: Progress and Prospects for the Future," Theriogenology 45:57-68 (1996) ("Wall")**

The PTO relies on Wall to support the assertion that transgene expression is unpredictable. While Wall indicates transgene expression for novel constructs may vary, Wall states, "Transgenes are expressed in only about half of transgenic lines, though some specific transgenes are expressed in a higher proportion (citations)." One of the citations relied upon by Wall to support "higher proportion" is Grovsfeld F. et al., "Position-independent, high level expression of the human beta-globin gene in transgenic mice," Cell 51:975-985 (1987). A review of this publication indicates that the locus that would be used by one skilled in the art when practicing the claimed subject matter provides site independent expression as a transgene construct. This paper, published nearly 10 years prior to the present priority application, supports Applicants position that human hemoglobin transgene constructs will predictably express in mammals other than humans.

**(iii) Kappel et al., "Regulating Gene Expression in Transgenic Animals," Current Opinions In Biotechnology, 3:548-553 (1992) ("Kappel").**

Kappel reviews the state of the art prior to 1992, which has little relevance to the state of the art in 1996. However, Kappel distinguishes the B-globin locus control region from other types of enhancer and promoter regions, just as Mullins and Wall. Kappel relies on the Grosveld publication when making this distinction.

***(b) Beta globin locus has been shown to express transgenically***

Thus, as evidenced by the publications cited by the Examiner the beta globin locus is a highly predictable locus with respect to trangene expression. This conclusion is also supported by Dr. Townes in his declaration where he states, "The Beta Globin Locus Control Region (LCR) sequences provide high level, position independent expression. As referenced in Mullins and Mullins above, LCRs have been used to express transgenes at high levels in species other than mice. In particular, the Beta Globin LCR has been used to produce high levels of human alpha and beta globin in transgenic pigs (See Swanson et al., and Sharma et al., Appendix A and B))." (Townes Declaration 2)

**(4) Mouse expression and phenotype predict results in other mammals**

The fact that applicants were able to get the disclosed methods and compositions to work in a mouse is predictive of whether these methods and compositions will work in other mammals because once it was shown that a mouse could live on human hemoglobin, which is a mammal evolutionarily distant from humans, other mammals would be expected work. Prior to Applicants making the disclosed mouse and other mammals, there was not a reasonable expectation of success that one mammal could live on another mammal's globin genes. The issue that was not addressed prior to the disclosed invention, was whether any mammal could live on any other mammal's hemoglobin alone. However, since the physiology of the mouse is very different than the physiology of other mammals, such as porcine or bovine, once a mouse was shown to be able to survive on human hemoglobin alone, it would be predicted that other mammals would also be able to survive on non-native hemoglobin. Dr. Townes states in his declaration "The production of mice that survive on human hemoglobin is predictive of the survival of larger mammals. The physiology of the mouse is more different from humans than is

the physiology of the cow or sheep and humans. The high metabolic rate of the mouse requires efficient oxygen delivery and the oxygen affinity of mouse and humans are significantly different. Therefore, we could not predict that the mouse would survive on human hemoglobin. However, the fact that mice did survive exclusively on human hemoglobin makes it likely that large animals would also survive solely on human hemoglobin." (Townes Declartation 2).

*3. Specification enables non-switching constructs*

The PTO indicates that the disclosed compositions require a DNA switch construct. This is generally incorrect. A switch construct is not needed for transgenes, but is helpful for transgenes related to sickle cell hemoglobin. As is discussed in the application at page 25, lines 5-14, the switch construct is used to offset the effect of the transgenic sickle hemoglobin in the early developmental stages of the mouse, when reduced oxygen capacity may not be tolerated like it is an adult. As explained by Dr. Townes, the switching construct is not needed in most constructs, because for example, fetal development is unaffected by reliance on only β-globin for example, rather than fetal γ-globin at the early stages of development. (Townes Declaration 2) Dr. Townes states, "Switching constructs are not required for all hemoglobin transgenes. We used a construct that switches from human gamma (fetal) to human beta (adult) globin during development when producing our mouse model of sickle cell disease. In this case, the production of human fetal hemoglobin is important to inhibit red cell sickling during fetal development and in new born animals. When a normal adult beta globin gene is linked to the LCR, normal adult hemoglobin is synthesized in the fetus and newborn and these animals are normal." (Townes Declaration 2). Thus, contrary to the position of the PTO the claims are not too broad, relative to the switching construct because a switching construct is not needed for operability of the full breadth of the claim.

**C. Rejection Under 35 U.S.C. § 103**

The Office Action dated July 20, 1999, rejected claims 1-19 under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty et al., "Lethal a-thalassaemia created by gene targeting in mice and its genetic rescue," Nat Genet., 11(1):33-9 (1995) ("Paszty"), and Ciavatta et al. "Mouse model of human $\beta^{o}$ thalassemia:Targeted deletion of the mouse $\beta^{maj}$ - and $\beta^{min}$-globin genes in embryonic stem cells," Proc. Natl. Aced. Sci. USA 92:9259-9263 (1995) ("Ciavatta")

taken with Rubin et al., :hypoxia-induced in Vivo Sickling of Transgenic Mouse Red Cells," J. Clin. Invest., 87:639-47 (1991) ("Rubin"), and Fabry et al. "A Second Generation Transgenic Mouse Model Expressing Both Hemoglobin S (HbS) and HbS-Antilles Results in Increased Phenotypic Severity," Blood, 86:2419-28 (1995) ("Fabry").

The Office Action dated July 20, 1999, also rejected claims 21-24 under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty and Ciavatta taken with Rubin et al. and Fabry in further view of Westphal, "Tansgenic mammals and biotechnology," FASEB J., 3(2):117-20 (1989) ("Westphal").

Claims 1-19 are not obvious over Pastzy and Ciavatta in view of Rubin and Fabry. The standard for obviousness requires both a motivation to arrive at the claimed subject matter as well as a reasonable expectation of success that the claimed subject matter would work. A motivation to try is not sufficient. A prima facie case of obviousness has not been provided because no motivation in any of the cited references, or in the art as a whole, has been provided. Furthermore, even if there was a motivation to make the claimed animals, those of skill in the art would not have had a reasonable expectation of success that the claimed mammals would live. Even if one assumes that there would have been motivation to make the claimed animals by mating the mice of Ciavatta and Paszty together, there is no reasonable expectation that these mice would live. In fact, as indicated by Dr. Townes, it was thought that mice would be unable to live on non-native hemoglobin alone. Dr. Townes states, "The production of mice that survive on human hemoglobin is predictive of the survival of larger mammals. The physiology of the mouse is more different from humans than is the physiology of the cow or sheep and humans. The high metabolic rate of the mouse requires efficient oxygen delivery and the oxygen affinity of mouse and humans are significantly different. Therefore, we could not predict that the mouse would survive on human hemoglobin. However, the fact that mice did survive exclusively on human hemoglobin makes it likely that large animals would also survive solely on human hemoglobin." (Townes Declaration 2).

Applicants also note the Office Action has set out many factors that would not have made the invention obvious. In this regard, the Office Action states, "in view of the . . . underdeveloped state of the ES cell art for species of mammals other than mice, the

unpredictable state of the art with respect to the generation of transgenic non-human mammals of all species expressing identical levels of a transgene and developing identical phenotypes due to such expression . . . it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed with a reasonable expectation of success." Office Action at 7-8. Therefore, Applicants respectfully traverse this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

**D. Double Patenting rejection**

***1. Statutory double patenting***

The Examiner provisionally rejected claims 1-14, 19, 21, 23, and 24 under 356 U.S.C. § 101 for allegedly claiming the same invention as that of claims 1-15 and 17-19 of co-pending Application NO. 08/934,385. After allowable subject matter, but for the double patenting rejection, is found in either the present application or 08/934,385 Applicants will address the statutory double patenting rejection, should it still be warranted, though claim cancellation.

***2. Non-statutory double patenting***

The Examiner provisionally rejected claims 15-18 and 22 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 and 17-19 of co-pending Application No. 08/934,385. After allowable subject matter, but for the non-statutory double patenting rejection, is found in either the present application or 08/934,385 Applicants will address the statutory double patenting rejection, should it still be warranted, though claim cancellation or the filing of a terminal disclaimer.

No additional fees are believed due, however, the Commissioner is hereby authorized to change any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EXPRESS MAIL

I hereby certify that this correspondence and anything indicated as attached or enclosed is being deposited with the United States Postal Service as Express Mail No. EL924195411US in an envelope addressed to: Commissioner for Patents, Box RCE, Washington, D.C. 20231, on the date shown below.

David E. Huizenga

April 10, 2002
Date